METHOD FOR PREVENTION AND/OR TREATMENT OF RHEUMATOID ARTHRITIS

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ABSTRACT

The invention provides a method for the prevention and/or treatment of rheumatoid arthritis, characterized in that the method comprises administering an IL-1β inhibitor and a calcineurin inhibitor, and a preventive and/or therapeutic medicine for rheumatoid arthritis including an IL-1β inhibitor and a calcineurin inhibitor in combination.

According to the invention, there can be provided a medicine and method for treating rheumatoid arthritis which exhibits suppressed side effects and excellent potency for suppression of arthritis.
Fig 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Edema Index</th>
<th>Percent edema suppression (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>7</td>
<td>18.5%</td>
</tr>
<tr>
<td>Drug A 3mg/kg</td>
<td>6.5</td>
<td>30.9%</td>
</tr>
<tr>
<td>Drug A + Drug B 0.3mg/kg</td>
<td>5.5</td>
<td>1.4%</td>
</tr>
<tr>
<td>Drug B 0.1mg/kg</td>
<td>5</td>
<td>11.2%</td>
</tr>
<tr>
<td>Drug B 0.3mg/kg</td>
<td>5</td>
<td>26.4%</td>
</tr>
<tr>
<td>Drug B 1mg/kg</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>
METHOD FOR PREVENTION AND/OR TREATMENT OF RHEUMATOID ARTHRITIS

TECHNICAL FIELD

[0001] The present invention relates to a method for the prevention and/or treatment of rheumatoid arthritis.

BACKGROUND ART

[0002] Rheumatoid arthritis is a disease which involves inflammation in many joints, concomitant with swelling and pain. When rheumatoid arthritis has progressed for a long period of time, the patient suffers irreversible deformity in the joints and functional disorders, and quality of life (QOL) of the patient is deteriorated considerably. In Japan, 0.6% of the total population and 1% of the population over age 30 suffer rheumatoid arthritis. With the progressive aging of society in recent years, elderly patients of rheumatoid arthritis have gradually increased in number.

[0003] Rheumatoid arthritis progresses through the following four stages. In the initial stage, joint pain and arthritis are observed, but the patient cannot be definitely diagnosed as suffering rheumatoid arthritis. In the early stage, the patient can be definitely diagnosed as suffering rheumatoid arthritis, but exhibits no or slight irreversible deformity (early stage of rheumatoid arthritis generally refers to a stage for 1 to 2 years from the onset thereof). In the progressive stage, the patient exhibits irreversible deformity and significant systemic symptoms, including fatigue, low-grade fever, and weight loss. In the late stage, arthritis has been almost sedated, but irreversible deformity such as deformity/contracture remains, resulting in pain and functional disorders as predominant symptoms. The method for the treatment varies depending on the corresponding stage of rheumatoid arthritis. The onset mechanism of rheumatoid arthritis has not yet been elucidated, although some studies report a relationship between the onset and a factor such as a hereditary factor or an acquired factor (an infectious disease). Therefore, complete prevention and curing of rheumatoid arthritis cannot be attained.

[0004] Thus, at present, treatment goals of rheumatoid arthritis are in early establishment of diagnosis as rheumatoid arthritis and suppressing inflammation caused by rheumatoid arthritis as soon as and as effectively as possible, whereby expression or progress of irreversible deformity is prevented so as to enhance QOL of patients from physical, mental, and social aspects. In this connection, upon the treatment of rheumatoid arthritis, the patients are well instructed in advance in terms of characteristics and the treatment of the disease, and receive a variety of treatment means such as physical therapy, kinesitherapy, drug therapy, and surgery.

[0005] In drug therapy, drugs such as non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDS), and steroids are employed in clinical settings. Recently, a biologics such as an antibody against an inflammatory cytokine as a target is also employed (Non-Patent Document 1).

[0006] A calcineurin inhibitor has been conventionally employed as an immunosuppressant. Known calcineurin inhibitors are cyclosporin (see Patent Document 1), tacrolimus (see Patent Document 2), ISA-247 (see Patent Document 3), 7-oxabicyclo[2.2.1]heptan-2,3-dicarboxylate derivatives (see Patent Document 4), INCA compounds (see Non-Patent Document 2), etc. Among calcineurin inhibitors, tacrolimus has been approved as a new DMARD in recent years (April, 2005). Tacrolimus has an action mechanism which differs from that of a conventional drug for the treatment of rheumatoid arthritis. Therefore, tacrolimus is a candidate as an effective therapeutic drug for rheumatoid arthritis of patients who have not sufficiently cured by a conventional drug. However, tacrolimus must be used carefully, due to adverse side effects such as renal disorders, hypertension, and diabetes.

[0007] In many diseases such as rheumatoid arthritis, osteoarthritis, osteoporosis, inflammatory colitis, immune deficiency syndrome, ichorhemia, hepatitis, nephritis, ischemic diseases, insulin-dependent diabetes, arterial sclerosis, Parkinson’s disease, Alzheimer’s disease, and leukemia, stimulation of production of interleukin 1β (IL-1β), which is an inflammatory cytokine, is observed. IL-1β is known to induce synthesis of enzymes which are conceived to be involved in inflammation; e.g., collagenase, COX, and PLA2, and to cause articular damage very similar to that caused by rheumatoid arthritis when intra-articularly injected to animals. Thus, IL-1β inhibitors are studied and developed to serve as drugs for the treatment of inflammatory diseases. Specifically, hitherto, there have been known bio-substances such as IL-1 receptor antagonist (see Non-Patent Document 3) and IL-1β antibodies (see Patent Documents 5, 6, and 7); and low-molecular-weight compounds such as T-614 (see Non-Patent Document 4); S-2474 (see Non-Patent Document 5), 2-benzyl-5-(4-chlorophenyl)-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one (see Patent Document 8); FR133605 (see Non-Patent Document 6), a halomethylamide derivative (see Patent Document 9), a pyrrolidine derivative (see Patent Document 10), and anaminobenzophenone derivatives (see patent Documents 11, 12, and 13).

[0008] Pathological conditions of rheumatoid arthritis vary considerably among patients in terms of age, stage, complications, side effects, QOL, etc. Hitherto, an ultimate therapeutic drug therefor has not yet been developed. Even though a therapeutic drug can control the disease condition, in some cases, the effect of the drug is suddenly lost, in a phenomenon called “escape phenomenon.” Under such circumstances, when drug therapy is performed, change of drugs and combined use of drugs are generally employed. Thus, clinical studies on the mode of use of such drugs are carried out extensively.

[0009] Meanwhile, hitherto, nothing has been known the effect of combined use of a calcineurin inhibitor and an IL-1β inhibitor.

Patent Document 2: WO 00/007594, pamphlet

DISCLOSURE OF THE INVENTION

[0011] Thus, an object of the present invention is to provide a medicine and method for the prevention and/or treatment of rheumatoid arthritis, which medicine and method exhibits suppressed side effects and excellent potency for suppression of arthritis.

[0012] Yet another object of the invention is to provide, for avoiding the escape phenomenon, an alternative drug therapy and combinatory use means.

[0013] In view of the foregoing, the present inventors have conducted extensive studies, and have found that use in combination of an IL-1β inhibitor and a calcineurin inhibitor provides an excellent effect of preventing arthritis. The present invention has been accomplished on the basis of this finding.

[0014] Accordingly, the present invention provides a preventive and/or therapeutic medicine for rheumatoid arthritis, the medicine comprising an IL-1β inhibitor and a calcineurin inhibitor in combination.

[0015] The present invention also provides a method for the prevention and/or treatment of rheumatoid arthritis, characterized in that the method comprises administering an IL-1β inhibitor and a calcineurin inhibitor.

[0016] The present invention also provides use of an IL-1β inhibitor and a calcineurin inhibitor for production of a preventive and/or therapeutic medicine for rheumatoid arthritis.

[0017] Since the medicine according to the present invention exhibits suppressed side effects and excellent potency for suppression of arthritis, the medicine is useful for the prevention and/or treatment of rheumatoid arthritis.

BRIEF DESCRIPTION OF THE DRAWING

[0018] [FIG. 1] A graph showing Edema indices of rats of a collagen-induced arthritis model measured, the rats being divided into a control group (group of no drug administration), an administration group (2-benzyl-5-(4-chlorophenyl)-6-(4-methylthio)phenyl)-2H-pyridazin-3-one (Drug A): 3 mg/kg, a combined administration group (Drug A: 3 mg/kg and tacrolimus (calcineurin inhibitor, Drug B): 0.3 mg/kg), and administration groups (Drug B: 0.1, 0.3, and 1 mg/kg).

BEST MODES FOR CARRYING OUT THE INVENTION

[0019] Examples of the IL-1β inhibitor employed in the present invention include biogenic substances such as IL-1 receptor antagonist and IL-1β antibodies; and low-molecular-weight compounds such as T-614, S-2474, 2-benzyl-5-(4-chlorophenyl)-6-(4-methylthio)phenyl)-2H-pyridazin-3-one, FR133605, a halomethylamine derivative, a pyridoline derivative, and an aminobenzophenone derivative. Of these, 2-benzyl-5-(4-chlorophenyl)-6-(4-methylthio)phenyl)-2H-pyridazin-3-one is particularly preferred.

[0020] 2-benzyl-5-(4-chlorophenyl)-6-(4-methylthio) phenyl)-2H-pyridazin-3-one employed in the present invention may be produced through the method disclosed in WO 99/025697 (patent document) or a similar method. Specifically, p-chlorophenylaetic acid is reacted with thiouanisole in the presence of a condensing agent such as polyphosphoric acid, to thereby form 2-(4-chlorophenyl)-4’-(methylthio)acetophenone. The thus-formed 2-(4-chlorophenyl)-4’-(methylthio) acetophenone is reacted with a base such as potassium t-butoxide in tetrahydrofuran, followed by adding ethyl bromoacetate to the reaction system, to thereby form ethyl 2-(4-chlorophenyl)-4’-(methylthio)phenyl)-4-oxobutanate. The thus-formed ethyl 2-(4-chlorophenyl)-4’-(methylthio)phenyl)-4-oxobutanate is reacted with hydrazine hydrate in ethanol, to thereby form 5-(4-chlorophenyl)-6-(4-(methylthio)phenyl)-4,5-dihydro-2H-pyridazin-3-one. The thus-formed 5-(4-chlorophenyl)-6-(4-(methylthio)phenyl)-4,5-dihydro-2H-pyridazin-3-one is reacted with benzy1 bromide in a solvent such as N,N-dimethylformamide in the presence of a base such as potassium carbonate, to thereby yield 2-benzyl-5-(4-chlorophenyl)-6-(4-(methylthio)phenyl)-2H-pyridazin-3-one.

[0021] Examples of the calcineurin inhibitor employed in the present invention include cyclosporin, tacrolimus, ISA-247, 7-oxa-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid derivatives, and INCA compounds. Among them, tacrolimus is particularly preferred. A commercial tacrolimus product such as a product of Astellas Pharma Inc. may also be employed in the invention.

[0022] As shown in the Example given hereinafter, both hindlimb edema can be synergistically suppressed through administration, in combination, of an IL-1β inhibitor (e.g., 2-benzyl-5-(4-chlorophenyl)-6-(4-methylthio)phenyl)-2H-pyridazin-3-one) and a calcineurin inhibitor (e.g., tacrolimus), whereby arthritis can be suppressed. Therefore, a medicine comprising an IL-1β inhibitor and a calcineurin inhibitor in combination is useful for a preventive and/or therapeutic medicine for rheumatoid arthritis, particularly for rheumatoid arthritis involving inflammation of a joint.

[0023] In the method according to the present invention for the prevention and/or treatment of rheumatoid arthritis and the preventive and/or therapeutic medicine according to the present invention for rheumatoid arthritis, the mass ratio of IL-1β inhibitor to calcineurin inhibitor is preferably 300:1 to 1:1, particularly preferably 100:1 to 3:1, from the viewpoint of a synergistic arthritis suppression action.

[0024] The preventive and/or therapeutic medicine according to the present invention for rheumatoid arthritis may be provided as a kit including a medicine containing an IL-1β inhibitor and a medicine containing a calcineurin inhibitor. Alternatively, the medicine according to the present invention may be provided as a combination preparation containing an IL-1β inhibitor and a calcineurin inhibitor. In other words, the IL-1β inhibitor and calcineurin inhibitor of the present invention may be administered simultaneously or separately with a predetermined interval, or administered as a combination preparation.
No particular limitation is imposed on the mode of administering the medicine of the present invention, and the mode may be appropriately selected in accordance with the purpose of the treatment. In oral administration, tablets, capsules, granules, film-coated drugs, powders, and syrups may be employed. In parenteral administration, injections, suppositories, inhalations, percutaneous drugs, eye drops, and nasal drops may be employed. Of these, oral administration is preferred.

The pharmaceutical products suited for the above modes of administration may appropriately be employed with the pharmaceutically acceptable carriers as exemplified below: vehicles and bulking agents such as starch, lactose, sucrose, mannitol, and silicic acid; disintegrants such as agar, calcium carbonate, potato or tapioca starch, alginic acid, and specific complex silicate salts; binders such as hydroxypropyl methyl cellulose, alginate salts, gelatin, polyvinylpyrrolidone, sucrose, and acacia; lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; diluents such as lactose and corn starch; buffers such as organic acids (e.g., citric acid, phosphoric acid, tartaric acid, and lactic acid), inorganic acids (e.g., hydrochloric acid), alkali hydroxides (e.g., sodium hydroxide and potassium hydroxide), and amines (e.g., triethanolamine, diethanolamine, and disopropanolamine); antiseptic agents such as p-oxybenzoyl esters and benzalkonium chloride; emulsifying agents such as anionic surfactants (e.g., calcium stearate, magnesium stearate, and sodium lauryl sulfate), cationic surfactants (e.g., benzalkonium chloride, benzethonium chloride, and cettylyricinum chloride), and nonionic surfactants (e.g., glycerol monostearate, sucrose fatty acid esters, polyoxyethylenehardened castor oil, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene fatty acid esters, and polyoxyethylenealkyl ethers); and stabilizing agents such as sodium sulfate, sodium bisulfate, dibutylhydroxytoluene, butylhydroxyanisole, and EDTA. In addition, additives such as an odor-suppressor, a dispersant, a preservative, and a flavoring may appropriately be used in accordance with needs.

Among the ingredients of the medicine according to the present invention, the IL-1β inhibitor (e.g., 2-benzyl-5-(4-chlorophenyl)-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one) is administered at a dose which is appropriately selected in accordance with the body weight, age, sex, condition, etc. of a patient in need thereof. Generally, the daily dose per adult is 2 to 320 mg, preferably 4 to 160 mg. The calcineurin inhibitor (e.g., tacrolimus) is administered at a dose which is appropriately selected in accordance with the body weight, age, sex, condition, etc. of a patient in need thereof. Generally, the daily dose per adult is 0.06 to 5 mg, preferably 1.5 to 3 mg. The ingredients may be administered in a single dose per day, or in two or more daily doses in a divided manner.

EXAMPLES

The present invention will next be described in more detail by the following examples, which shall not be construed as limiting the invention thereto.

Example 1

The effect on suppressing both-hindlimb edema of 2-benzyl-5-(4-chlorophenyl)-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one (synthesized through the aforesaid method) and that of tacrolimus (Prograf (injection: 5 mg), product of Fujisawa Pharmaceutical Co., Ltd.) were determined both in the cases of combined administration and sole administration through the following procedure (by use of rats of a collagen-induced arthritis model) (FDA, CBDR, CDFR, CDRI: Guidance for industry—Clinical development programs for drugs, devices, and biological products for the treatment of rheumatoid arthritis (RA)—(1990)). Lewis female rats (LEW/Cr) (obtained from Charles River Laboratories Japan, Inc.) were employed as test animals.

For each 8-week-old LEW/Cr rat, the volume of a portion from the ankle to the toe tip of each hindlimb was measured by means of a plethysmometer for small animals (TK-101CMP, product of Unicon), and a total of the two volumes was employed as a volume of the hindlimbs (hereinafter referred to as both-hindlimb volume) at the start of the test (hereinafter referred to as Pre value). By use of the Pre value as an index, the rats were divided into groups which are alike from group to group, through one-parameter-based block randomization.

The collagen emulsion for sensitization employed for inducing arthritis in rats was prepared by homogenizing a 0.3% Type II collagen liquid (product of Collagen Research Center), adjuvant peptide (product of Peptide Institute, Inc.), and adjuvant incompete Freund (product of DIFCO) by means of a Handy Micro Homogenizer (product of Microtec Niton) under cooling with ice. The thus-prepared emulsion was intracutaneously injected to 10 sites in the dorsum of each rat at 0.1 ml/site, to thereby initially sensitize the rat.

Seven days after initial sensitization, the same emulsion (0.12 ml) was intracutaneously injected to the tail head of the rat for booster sensitization.

Administration of one drug or two drugs was carried out the day after initial sensitization to day 26. To the 2-benzyl-5-(4-chlorophenyl)-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one solo administration group, the drug was orally administered twice; in the morning (9:00 to 11:00) and in the evening (15:30 to 17:30) at a dose of 3 mg/kg. To the tacrolimus sole administration group, the drug was orally administered once in the afternoon (11:30 to 13:30) at a dose of 0.1, 0.3, or 1 mg/kg. To the combined administration group (2-benzyl-5-(4-chlorophenyl)-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one and tacrolimus), 2-benzyl-5-(4-chlorophenyl)-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one was orally administered in the morning (6:00 to 11:00) and in the evening (15:30 to 17:30) at a dose of 3 mg/kg, and tacrolimus was orally administered in the afternoon (11:30 to 13:30) at a dose of 0.3 mg/kg.

Fourteen days, 18 days, 22 days, and 26 days after initial sensitization, both-hindlimb volume was measured. Volume of both-hindlimb edema was calculated by subtracting the Pre value from the thus-measured value. The sum of the volumes of both-hindlimb edema at days 14, 18, 22, and 26 after initial sensitization was employed as a Edema Index, which was used as the index for assessing the potency of the drug(s).

Table 1 and FIG. 1 show Edema Index of the groups of rats, the groups being the 2-benzyl-5-(4-chlorophenyl)-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one solo administration group, the tacrolimus solo administration group, and the combined administration group. The Edema Index of each group is an average of the indices obtained from 6 to 12 rats ± standard error. Percent edema suppression represents a value obtained from the relation:

\[
\text{Percent edema suppression} = \left(1 - \frac{\text{average both-hindlimb edema volume of the control group}}{\text{average both-hindlimb edema volume of each}}\right) \times 100\%
\]
administration group) /
(average both-hindlimb edema volume of the control group). Relative factor represents a ratio of 
(average both-hindlimb edema volume of each administration 
group) /
(average both-hindlimb edema volume of the control group).

[0035] As a result, solo administration of 2-benzyl-5-(4-
chlorophenyl)-6-[4-(methylthio)phenyl]-2H-pyridazin-3-
one and that of tacrolimus (up to 1 mg/kg) do not result in 
potent Edema Index suppression effects.

[0036] In contrast, combined administration of both drugs 
exhibits a potent effect on reducing Edema Index, and its 
effect is higher than that obtained through administration of 
tacrolimus 1 mg/kg. The relative factor of Edema Index of 
the group of combined administration of both drugs is smaller 
than the product of the relative factors of the solo 
administration groups, indicating that a clear synergistic effect can be 
a attained through combined administration.

### TABLE 1

<table>
<thead>
<tr>
<th>Tested drugs</th>
<th>Edema Index (mL)</th>
<th>Percent edema suppression (%)</th>
<th>Relative factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>6.85 ± 0.33</td>
<td>19</td>
<td>0.81</td>
</tr>
<tr>
<td>2-benzyl-5-(4-chlorophenyl)-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one solo administration group (3 mg/kg)</td>
<td>5.58 ± 0.03</td>
<td>31</td>
<td>0.69</td>
</tr>
<tr>
<td>2-benzyl-5-(4-chlorophenyl)-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one (3 mg/kg) and tacrolimus (0.3 mg/kg) combined administration group</td>
<td>4.73 ± 0.20</td>
<td>31</td>
<td>0.69</td>
</tr>
<tr>
<td>Tacrolimus solo administration group (0.1 mg/kg)</td>
<td>6.75 ± 0.31</td>
<td>1</td>
<td>0.99</td>
</tr>
<tr>
<td>Tacrolimus solo administration group (0.3 mg/kg)</td>
<td>6.09 ± 0.30</td>
<td>11</td>
<td>0.89</td>
</tr>
<tr>
<td>Tacrolimus solo administration group (1 mg/kg)</td>
<td>5.04 ± 0.20</td>
<td>26</td>
<td>0.74</td>
</tr>
</tbody>
</table>

Product of relative factors of solo administration groups: 0.81 × 0.89 = 0.72
Both-hindlimb edema volume of each group is an average of the volumes obtained from 6 to 12 rats ± a standard error.

1. A preventive and/or therapeutic medicine for rheumatoid arthritis, the medicine comprising an IL-1β inhibitor and a calcineurin inhibitor in combination.

2. A preventive and/or therapeutic medicine for rheumatoid arthritis as described in claim 1, wherein the rheumatoid arthritis involves inflammation of a joint.

3. A preventive and/or therapeutic medicine for rheumatoid arthritis as described in claim 1 or 2, wherein the IL-1β inhibitor is 2-benzyl-5-(4-chlorophenyl)-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one.

4. A preventive and/or therapeutic medicine for rheumatoid arthritis as described in any one of claims 1 to 3, wherein the calcineurin inhibitor is tacrolimus.

5. A preventive and/or therapeutic medicine for rheumatoid arthritis as described in any one of claims 1 to 4, wherein the medicine is for peroral administration.

6. A method for the prevention and/or treatment of rheumatoid arthritis, characterized in that the method comprises administering an IL-1β inhibitor and a calcineurin inhibitor.

7. The method for the prevention and/or treatment of rheumatoid arthritis as described in claim 6, wherein the rheumatoid arthritis involves inflammation of a joint.

8. The method for the prevention and/or treatment of rheumatoid arthritis as described in claim 6 or 7, wherein the IL-1β inhibitor is 2-benzyl-5-(4-chlorophenyl)-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one.

9. The method for the prevention and/or treatment of rheumatoid arthritis as described in any one of claims 6 to 8, wherein the calcineurin inhibitor is tacrolimus.

10. The method for the prevention and/or treatment of rheumatoid arthritis as described in any one of claims 6 to 9, wherein said administering is carried out through oral administration.

11. Use of an IL-1α inhibitor and a calcineurin inhibitor for production of a preventive and/or therapeutic medicine for rheumatoid arthritis.

12. Use as described in claim 11 for production of a preventive and/or therapeutic medicine for rheumatoid arthritis, wherein the rheumatoid arthritis involves inflammation of a joint.

13. Use as described in claim 11 or 12 for production of a preventive and/or therapeutic medicine for rheumatoid arthritis, wherein the IL-1β inhibitor is 2-benzyl-5-(4-chlorophenyl)-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one.

14. Use as described in any one of claims 11 to 13 for production of a preventive and/or therapeutic medicine for rheumatoid arthritis, wherein the calcineurin inhibitor is tacrolimus.

15. Use as described in any one of claims 11 to 14 for production of a preventive and/or therapeutic medicine for rheumatoid arthritis, wherein the preventive and/or therapeutic medicine for rheumatoid arthritis is for oral administration.

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